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Functional effects of somatostatin receptor 1 activation on synaptic transmission in the mouse hippocampus

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Abstract

Somatostatin-14 (SRIF) co-localizes with GABA in the hippocampus and regulates neuronal excitability. A role of SRIF in the control of hippocampal activity has been proposed, although the exact contribution of each SRIF receptor (sst_1–sst_5) in mediating SRIF action requires some clarification. We used hippocampal slices of wild-type and sst_1 knockout (KO) mice and selective pharmacological tools to provide conclusive evidence for a role of sst_1 in mediating SRIF inhibition of synaptic transmission. With single- and double-label immunohistochemistry, we determined the distribution of sst_1 in hippocampal slices and we quantified sst_1 colocalization with SRIF. With electrophysiology, we found that sst_1 activation with CH-275 inhibited both the NMDA- and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-mediated responses. Results from sst_1 KO slices confirmed the specificity of CH-275 effects; sst_1 activation did not affect the inhibitory transmission which was in contrast increased by sst_4 activation with L-803,087 in both wild-type and sst_1 KO slices. The AMPA-mediated responses were increased by L-803,087. Functional interaction between sst_1 and sst_4 is suggested by the finding that their combined activation prevented the CH-275-induced inhibition of AMPA transmission. The involvement of pre-synaptic mechanisms in mediating inhibitory effects of sst_1 on excitatory transmission was demonstrated by the finding that CH-275 (i) increased the paired-pulse facilitation ratio, (ii) did not influence the AMPA depolarization in the presence of tetrodotoxin, and (iii) inhibited glutamate release induced by epileptiform treatment. We conclude that SRIF control of excitatory transmission through an action at sst_1 may represent an important contribution to the regulation of hippocampal activity.

Keywords: glutamate, hippocampal slices, somatostatin analogs, synaptic transmission, transgenic mice.

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The peptide somatostatin-14, or SRIF (somatotropin release-inhibiting factor), is expressed by hippocampal interneurons and plays an important inhibitory role on excitatory activity including epilepsy (see Tallent and Qiu 2008). Information on the precise contribution of each SRIF receptor subtype (sst_1–sst_5) on the SRIF-induced inhibition of hippocampal activity is still limited. In epileptic models, for instance, there is indication that sst_2 and sst_4 may mediate the majority of SRIF antiepileptic actions, with a main role of sst_2 in rat and of sst_4 in mouse (Qiu *et al.* 2008; see for ref Tallent and Qiu 2008). On the other hand, there are also data suggesting excitatory actions of sst_4 on seizure susceptibility and hippocampal excitatory neurotransmission in rodents (Moneta *et al.* 2002; Cammalleri *et al.* 2004). In addition, a role of sst_1 in mediating anticonvulsant effects of SRIF has been demonstrated in a mouse hippocampal model of interictal-like activity (Cammalleri *et al.* 2004) although this has been not confirmed by Qiu *et al.* (2008). There are also indications that SRIF receptors may mediate SRIF antiepileptic effects by modulating each other function. For instance, in the absence of sst_1, as in sst_1 knockout (KO)

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Abbreviations used: 4-AP, 4-aminopyridine; aCSF, artificial CSF; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AP, aminopyridine; APV, DL-2-amino-5-phosphonovalerate; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; EPSP, excitatory post-synaptic potential; ESI-MS, electrospray tandem mass spectrometry; IPSP, inhibitory post-synaptic potential; IR, immunoreactivity; KO, knockout; ND, numerical density; PB, phosphate buffer; PPF, paired-pulse facilitation; SP, somatic profiles; SRIF, somatotropin release-inhibiting factor/somatostatin; sst_{1-5}, SRIF receptor 1 through 5.TTX, tetrodotoxin; WT, wild-type.

